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BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER

BRISTOL, LYNN ANNE

ART UNIT	PAPER NUMBER
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1643

NOTIFICATION DATE	DELIVERY MODE
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03/11/2009

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 10/535,433	Applicant(s) FRIGERIO ET AL.	
	Examiner LYNN BRISTOL	Art Unit 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 December 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1 and 34-89 is/are pending in the application.
- 4a) Of the above claim(s) 45, 47, 49, 51 and 53-81 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 34-44, 46, 48, 50, 52 and 82-89 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/23/08 has been entered.
2. Claims 1 and 34-89 are all the pending claims for this application.
3. Claims 88 and 89 were added in the Response of 12/3/08.
4. Claims 45, 47, 49, 51 and 53-81 are withdrawn from examination.
5. The Response of 8/21/08 was entered in the Advisory Action of 9/11/08.
6. Claims 1, 34-44, 46, 48, 50, 52 and 82-89 are all the pending claims under examination.
7. This Office Action contains new grounds for objection and rejection.

Withdrawal of Objections

Specification

8. The objection to the specification for failing to provide sequence identifiers for the amino acid sequences on p. 8, lines 7 and 31 and p. 10, line 31 is withdrawn in view of the amendment to the specification of 8/21/08.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, second paragraph

9. The rejection of Claim 34 in lacking antecedent basis for the recitation “the immunoglobulin heavy chain molecule” was withdrawn in the Advisory Action of 9/11/08 based on the amendment of Claim 1 to recite “an immunoglobulin heavy chain molecule” in the Response of 8/21/08.
10. The rejection of Claim 44 in lacking antecedent basis for the recitation “method nucleotide sequence” was withdrawn in the Advisory Action of 9/11/08 based on the amendment of Claim 44 to recite “modified nucleotide sequence” in the Response of 8/21/08.
11. The rejection of Claims 39 and 44 for failing to include a period at the end of the claim was withdrawn in the Advisory Action of 9/11/08 based on the amendment of the claims to recite “modified nucleotide sequence” in the Response of 8/21/08.
12. The rejection of Claim 43 for the recitation in element (iii) “an isoleucine to amino acids from the C-terminus” was withdrawn in the Advisory Action of 9/11/08 based on the amendment of the claim to recite “isoleucine 2 amino acids from the C-terminus” in the Response of 8/21/08.

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13. The rejection of Claim 87 for reciting improper Markush group language was withdrawn in the Advisory Action of 9/11/08 based on the amendment of the claim to recite "is a member selected from" in the Response of 8/21/08.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

14. The rejection of Claims 1, 34-38, 40-44, 46, 48, 50, 52 and 82-87 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained.

The rejection was maintained in the Office Action of 1/25/08 as follows:

"Applicants' allegations on pp. 15-16 of the Response of 10/31/07 and the Declaration of Dr. Vitale have been considered but are not found persuasive.

In the Response, Applicants allege that a written description rejection should be rare; that the modification is only to be performed on the C-terminal 18 amino acids of the immunoglobulin heavy chain and all of the details for performing the modifications are taught in the specification on pp. 5, 6 and 8-12.

The examiner respectfully submits that any modification can be introduced into the 18 amino acid C-terminus of the heavy chain comprising a $\alpha 3$ or mu domain as the claims are interpreted. This could include, *for example*, any one or all of the modifications to any given nucleotide sequence recited in Claim 35:

- a) one or more point mutations
- b) one or more nucleic acid deletions
- c) one or more nucleic acid additions, *and*
- d) one or more nucleotides replaced with a synthetic nucleotide sequence.

If a given sequence were to include a modification for each of a-d, then Applicants have not demonstrated a single example of a species falling within the scope much less that the sequence would be reduced in vacuolar targeting signal ability and retain antigen binding activity.

Further, Claim 36 describes another example of a sequence where Xaa2 can be "*any amino acid*" irrespective of its charge, solubility, etc, (and 23 different amino acids exist for each possible substitution) and Applicants have not demonstrated a reasonable number of working embodiments in which "*any amino acid*" could be substituted in the Xaa2 position. A similar comparison can be made to Claims 44 (i.e., X9= *any amino acid*), 45

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(Xaa2= independently *any* amino acid), 82 (Xaa2= independently *any* amino acid), and 87 (which depends from Claim 44). Applicants have not demonstrated a reasonable number of species falling within the scope of these claims much less that the sequence would be reduced in vacuolar targeting signal ability and retain antigen binding activity.

The examiner's position is that the specification does not describe a reasonable number of embodiments falling within the scope of generic claim 1 or any one of Claims 35, 36, 44, 45 or 87, and which encodes a heavy chain comprising modified C-terminal 18 amino acids with a reduced or eliminated vacuolar targeting signaling and which still binds an antigen, to support the genus as claimed.

The Declaration of Dr. Vitale is not persuasive on several grounds.

First, Dr. Vitale effectively disavows any priority claim for subject matter of the instant application to the PCT filing date (11/17/2003) and the foreign priority date (11/18/2002). Dr. Vitale asserts that the filing date for the instant application is 5/18/05. It is noted that inasmuch as the instant application entered national stage on 5/18/05, Applicants did not perfect their 102(e) date until 2/2/06 when they filed the executed oath/declaration.

Secondly, Dr. Vitale avers that because only 18 amino acids of the C-terminal end of an immunoglobulin are required to be modified, "there is not an infinite number of possible mutations" and "a sufficient number of representative species of sequences" is demonstrated in the specification.

As discussed in the previous office action and above, Applicants have shown an antibody comprising a modified heavy chain comprising synthetic C-terminal regions for the α 3 domain comprising SEQ ID NOS: 7, 8, 9 or 69 and comprising a light chain, where the vacuolarization of the heavy chain is reduced or removed when the protein is expressed in transgenic plant cells, and the antibody molecule has specific binding ability for a given antigen in having both a heavy and light chain. Applicants have not shown a reasonable number of antibodies could be produced by the method as falling within the full scope of modifications to the C-terminus encompassed by the instant claims and which would also a) have reduced or removed vacuolarization when expressed in any kind of cell and b) retain antigen binding. For these reasons, the rejection is maintained."

The rejection was maintained in the Advisory Action of 9/11/08 as follows:

"Applicants allege the claims are directed to a method of making antibodies. Applicants allege the rejection is misplaced because the written description for following the method steps is taught in the specification and that in practicing those steps, the specification need not demonstrate that a reasonable number of working embodiments for modified antibodies are actually obtained.

Response to Arguments

The schematic provided in the response on p. 16 outlining the method steps fails to include the final step of screening for functional antibodies, where a functional antibody is required to meet the following criteria a) retains antigen binding, b) the vacuolar targeting signal encoded within the immunoglobulin heavy chain is removed or reduced in its effectiveness, and c) antibody secretion is improved. The data from Figures 6, 7, 9 and 10 shows that examples of C-terminal modified antibodies produced by the method were in fact further examined or screened to see whether antibody secretion was improved (i.e., the transport of the antibody to vacuole was reduced or eliminated). Further, the claim language in Claim 1, element (b) requires that the vacuolar targeting is removed or reduced, and thus absent further screening steps for working embodiments, it is not clear how the ordinary artisan could generate the genus of functional antibodies in view of the broad number of possible modifications introduced into the antibody format in following the method steps."

Applicants' allegations on pp. 13-14 of the Response of 12/23/08 have been considered and are not found persuasive. Applicants allege "But the Examiner's explanation went on to note that the "data from Figures 6, 7, 9 and 10 [of the Specification] shows that examples of C-terminal modified antibodies produced by the method were in fact further examined or screened to see whether antibody secretion

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was improved." Applicants submit the Examiner's own comments evidence the impropriety of the continued rejection, in that, the Examiner urges that there is insufficient written description for the claimed method while at the same time the Examiner points to portions of the Specification which indeed describe results of the claimed method."

Response to Arguments

The specification does not describe that in practicing the method, a reasonable number of antibody embodiments falling within the scope of generic claim 1 or any one of Claims 35, 36, 44, 45 or 87 are produced, and which comprise a heavy chain comprising modified C-terminal 18 amino acids with a reduced or eliminated vacuolar targeting signaling in plant cells and which retain antigen binding. The specification does not support the method for producing the genus of all possible modified antibodies as instantly claimed. As reiterated throughout the examination proceeding, Applicants generic claims specifically recite functional language for the genus of antibodies produced by the method, namely, "to remove, or reduce the effectiveness of, one or more vacuolar targeting signal of the encoded immunoglobulin heavy chain." Thus the ordinary artisan cannot separate the method from the product produced by that method: a) the structure function relationship for the antibodies produced by the method with respect to the modified heavy chain C-terminus, i.e., the modification conferring removal or reduction in the effectiveness of one or more vacuolar targeting signal of the encoded immunoglobulin heavy chain, and b) the ability of the antibody to bind a target antigen. MPEP 2163 states in part:

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“For example, if the art has established a strong correlation between structure and function, one skilled in the art would be able to predict with a reasonable degree of confidence the structure of the claimed invention from a recitation of its function. Thus, the written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function. In contrast, without such a correlation, the capability to recognize or understand the structure from the mere recitation of function and minimal structure is highly unlikely. In this latter case, disclosure of function alone is little more than a wish for possession; it does not satisfy the written description requirement. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 (written description requirement not satisfied by merely providing “a result that one might achieve if one made that invention”); *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming a rejection for lack of written description because the specification does “little more than outline goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate”). Compare *Fonar*, 107 F.3d at 1549, 41 USPQ2d at 1805 (disclosure of software function adequate in that art).”

MPEP 2105 states in part:

“The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see i)(A), above), reduction to drawings (see i)(B), above),

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or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406”, and

A “representative number of species” means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure “indicates that the patentee has invented species sufficient to constitute the gen[us]”, and

“A definition by function alone “does not suffice” to sufficiently describe a coding sequence “because it is only an indication of what the gene does, rather than what it is.” *Eli Lilly*, 119 F.3 at 1568, 43 USPQ2d at 1406. See also *Fiers*, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing *Amgen Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991)). An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties,

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and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004)."

Enablement

15. The rejection of Claims 1, 34-38, 40-44, 46, 48, 50, 52 and 82-86 (and new claims 88 and 89) under 35 U.S.C. 112, first paragraph, is maintained for lacking enablement for expressing a functional antibody having only a heavy chain much less any heavy chain with *any modified $\alpha 3$ or mu domain*, or any transgenic plant- or plant cell-expressed antibody having reduced or removed vacuolar targeting by introduction of just any synthetic nucleotide sequence or synthetic tail into the $\alpha 3$ or mu domain of the heavy chain or any $\alpha 3$ or mu domain-modified heavy chain expressed by the host and having retained specific antigen binding affinity in the absence of a light chain.

For purposes of review, the rejection was maintained in the Office Action of 1/25/08 as follows:

"A) Applicants' allegations on p. 17 of the Response of 10/31/07 and the Declaration of Dr. Vitale have been considered but are not found persuasive.

Applicants' allege that the specification and the one skilled in the art having a general knowledge such as an undergraduate biology student could practice the invention without undue experimentation.

The examiner submits that because the combination of potential modifications that could be made to the amino acid residues anywhere within the 18 C-terminal residues of a heavy chain comprising an alpha-3 or mu domain is innumerable, and because some residues can be substituted with "*any amino acid*" or the nucleotide encoding the amino acid sequence could comprise one or any combination of

- a) one or more point mutations
- b) one or more nucleic acid deletions
- c) one or more nucleic acid additions, *and*
- d) one or more nucleotides replaced with a synthetic nucleotide sequence,

that it would require undue experimentation for one of ordinary skill in the art to practice the invention. More guidance is required for one of ordinary skill in the art to reproduce the invention and render the reproducibility without undue burden.

Further, Applicants have not addressed the predictability factor in *Wands* which requires that one of skill in the art could predict based on the specification that a reasonable number of antibodies could be produced from any combination of modifications as presently recited in the claims. As discussed above, the specification is not enabling

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for making the full breath of embodiments where just "*any amino acid*" can be substituted into the C-terminus or the nucleotide encoding the amino acid sequence could comprise one or any combination of

- a) one or more point mutations
- b) one or more nucleic acid deletions
- c) one or more nucleic acid additions, *and*
- d) one or more nucleotides replaced with a synthetic nucleotide sequence.

An "undergraduate in biology" could not reasonably expect or predict that the heavy chain produced by the method would have reduced vacuolarization, proper folding with a light chain *and* antigen binding. For example, refer to the references of record describing the unpredictability of amino acid substitutions in protein chemistry in general (Ibragimova and Wade (Biophysical Journal, Oct 1999, Vol. 77, pp. 2191-2198); Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138); Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252); Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987); and Lin et al Biochemistry USA Vol 14:1559-1563 (1975)). It is well known in the art that when modifying an amino acid of a protein, one can expect the 3-dimensional denaturation of the protein.

The specification demonstrates that the NVSVSV sequence is responsible for the vacuolar targeting of the antibodies produced by plants, and more particularly by *Nicotiana tabacum*. Based on the specification, it is not clear whether the NVSVSV sequence has any chance of being recognized by plants other than *Nicotiana tabacum*. The method of Claim 1 encompasses expressing the antibody in any host cell, but it is not clear from the specification that vacuolar sorting signals would be the same between, for example, mammalian cells, yeast or plants. Absent a showing to the contrary (further experiments or supported reasoning), the specification is only enabling for the modified NVSVSV sequence for use in expressing antibodies, where the host cell is *Nicotiana tabacum*.

B) Applicants have not addressed the section of the Office Action where the examiner rejected the claims on the basis of producing only a single heavy chain antibody. In the Office Action, the examiner asserted that one of skill in the art recognized at the time of Applicant's filing date, that both heavy and light chains, or at least the full complement of CDRs from both a heavy and light chain, were required to be present in an antibody molecule in order for the antibody molecule to bind to the antigen of interest. The rejection was based in the breadth of the claims for producing only a heavy chain in the absence of a corresponding light chain or in the absence of the light chain CDRs. Thus the scope of Applicants claimed method encompasses producing a single heavy chain which allegedly is reduced in vacuolarization and retains antigen binding. Applicants should understand that implicit in producing the antibody molecule with reduced vacuolarization, is the requirement that the antibody molecule have a use under 112, 1st paragraph. It is the examiner's position that the heavy chain produced by the claimed method could not be used and therefore would not have a practical use, i.e., antigen binding, much less that it is unpredictable that the heavy chain alone would bind antigen, thus it is not clear how the claim scope encompassing producing modified single heavy chains would meet the requirements under 112, 1st paragraph.

Applicants' response is incomplete, and therefore the rejection is maintained."

The rejection was maintained in the Advisory Action of 9/11/08 as follows:

"Applicants allege the same rejection was made in *Ex parte Kubin*. Applicants excerpt *Kubin* for the aspect of the decision stating "the amount of experimentation to practice the full scope of the claimed invention might have been extensive, but it would have been routine. The techniques necessary to do so were well known to those skilled in the art." *Id* at 1416. Further, the Hunter et al. publication confirm that vacuole sorting signal sequences work across species.

Response to Arguments

The examiner respectfully submits that the facts and the claim scope in *Kubin* are unlike the instant case. The claims adjudicated in *Kubin* were directed to polynucleotides encoding polypeptides "at least 80% identical to amino acids 22-221 of SEQ ID NO:2' binding to "CD48." Here instant claim 1 is broader in scope than the claims in *Kubin*, because in *Kubin*, the extent of variation could be no more than 20% (or at least 80% identical). Here, there is no limitation as to what constitutes "the modifying" in the region of "the nucleotide sequence encoding the C-terminus 18 amino acids of the immunoglobulin heavy chain molecule." Further, there is no claimed requirement that the final product binds to any antigen. As stated in the Office Action of 1/25/08, the scope of the "modification" encompasses a) one or more point mutations; b) one or more nucleic acid deletions; c) one or more nucleic acid additions, and/or d) one or more nucleotides replaced with a synthetic nucleotide sequence."

Applicants allegations on p. 14 of the Response of 12/23/08 have been considered but are not found persuasive. Applicants allege “enclosed as Exhibit 1 is a flow chart that details the portions of the Specification that describe the steps of Applicants claimed method in a manner sufficient for one skilled in the art to make and use the claimed invention.”

Response to Arguments

Applicants urge the Office to believe that a claimed method is enabled because the specification as summarized in the one page exhibit is fully enabling for practicing the method invention. Additionally, Applicants are wrong in their understanding of the law for enablement under 35 U.S.C. 112, first paragraph. The specification must be enabling for making and using the invention. Applicants’ assertion that the antibodies are not required to have a function much less binding an antigen, or that the method as claimed does not require the product antibodies to have any function, is a legal falsehood. The same antibodies generated by the method must have a utility, otherwise what purpose would be served by practicing the method to produce the polypeptides? See MPEP 2138.05 citing *Birmingham v. Randall*, 171 F.2d 957, 80 USPQ 371, 372 (CCPA 1948) “To establish an actual reduction to practice of an invention directed to a method of making a product, it is not enough to show that the method was performed. “[S]uch an invention is not reduced to practice until it is established that the product made by the process is satisfactory, and [] this may require successful testing of the product.” The rejection is maintained because Applicants have not met their burden in

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responding to the grounds for rejection set forth under section A) in the Office Action of 1/25/08.

Applicants have abjectly ignored the Examiner's grounds for rejection set forth under section B) in the Office Action of 1/25/08. The claims read on producing single chain antibodies comprising only a heavy chain and therefore having a single variable domain, that in order to have a practicable use, is otherwise expected to bind an antigen. As stated by the Examiner throughout the prosecution proceeding, there is no enabling disclosure in the originally filed specification or the prior art (see Rudikoff cited in the Office Action of 6/21/07) for a single domain heavy chain antibody which retains antigen binding much less one in which the C-terminus of the heavy chain is modified in the 18 C-terminal, amino acids in order to remove or confer reduced vacuolar targeting of the protein chain in a host plant cell.

Smith-Gill et al. (J. Immunol. 139:4135-4144 (1987)) observed from chain recombination experiments that through interactions between the VH/VL pair, specificity for antigen is H chain determined, specific binding is increased when L chains of the same parental isotype are used, and that both H and L chains determine fine specificity.

Kumar et al. (J. Biol. Chem. 275:35129-35136 (2000)) discloses Fab molecules with anti-DNA (light chain) and anti-cardiolipin (heavy chain) binding activities, and that pairing of the partner chains is dependent on the particular H/L chain pairing.

Song et al. (Biochem Biophys Res Comm 268:390-394 (2000)) discloses that affinity and specificity of scFv for preS1 protein of HBV is dependent on S-S bond formation in conferring correct refolding of the fragments for retaining binding properties,

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and that L chains are predominant in antigen binding. Therefore, selecting and producing just any variable domain substituted antibody with the ability to properly associate and assemble into a fully functional antibody which maintains the binding specificity for the original antigen would be highly unpredictable based on the methods described in the specification and the prior art disclosures.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

16. The rejection of Claims 1, 34, 35, 38, 40, 41, 46, 48 and 50 under 35 U.S.C. 103(a) as being unpatentable over Frigerio et al. (Plant Physiology 123:1483-1493 (August 2000); cited in the IDS of May 18, 2005 and the PTO 892 form of 2/2/07) in view of Vitale and Raikhel (Trends in Plant Science 4(4):149-155 (April 1999); cited in the IDS of May 18, 2005 and the PTO 892 form of 2/2/07), Koide et al. (Plant Cell Physiol. 40(11):1152-1159 (1999); cited in the IDS of and the PTO 892 form of 2/2/07) and Matsuoka et al. (J. Exp. Bot. 50:165-174 (1999); cited in the IDS of 5/18/05) is maintained.

For purposes of review, the rejection was maintained in the Office Action of 1/25/08 as follows:

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"Applicants' allegations on pp. 18-19 of the Response of 10/31/07 and the Declarations of Drs. Vitale and Frigerio have been carefully considered but are not found persuasive.

The allegations that are presented are essentially that the named inventors at the time of the instant method invention were the first to realize *and* identify human proteins containing cryptic sorting signals that could be used to target human proteins to a particular location in plants.

The examiner respectfully disagrees with Applicants allegation that no knowledge or awareness of signaling sequences in human proteins existed in the prior art before or at the time of their invention. The knowledge of signaling sequences more especially in view of the Frigerio reference which fully contemplated the existence of cryptic sequence residues that mediated heterologous proteins in vacuole trafficking with the extrapolation of this possibility to the hybrid IgA/G antibodies used in their study belies Applicants assertion. The declarants have not addressed how or why *with* this information in the Frigerio reference, one skilled in the art would not have been motivated to have produced by plant expression methods an antibody that would not be sequestered in vacuoles but instead secreted in abundance by modifying the signal sequences. Thus the rejection is maintained.

The rejection was maintained in the Advisory Action of 9/11/08 as follows:

"Applicants allege element (b) of Claim 1 is not taught in the cited art references.

Response to Arguments

None the individual references taken alone teach the exact language in element (b) of Claim 1 but the claims are not patentably distinguishable in view of the combined disclosures because of the reasons set forth in the Office Action of 6/21/07, and further when considered under the recent KSR decision. Under the recent KSR decision, the cited references of art are not required to "explicitly teach or suggest" all of the steps or elements. The Supreme Court has determined in *KSR International Co. v. Teleflex, Inc.*, 550 U.S. __, 82 USPQ2d 1385 (2007), that "a person of ordinary skill attempting to solve a problem will" not "be led only to those elements of prior art designed to solve the same problem....." (KSR, 550 U.S. at __, 82 USPQ2d at 1397). In addition, the court found that "When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variant, 35 USC 103 likely bars its patentability" (KSR, 550 U.S. at __, 82 USPQ2d at 1396). Further the court found that the Federal Circuit has erred in applying the teaching-suggestion-motivation test in an overly rigid and formalistic way, in particular by concluding "that a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try'" (KSR, 550 U.S. at __, 82 USPQ2d at 1397) and has further determined that ".....[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results" (KSR, 550 U.S. at __, 82 USPQ2d at 1395). The court further found that "..... the conclusion that when a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious" (KSR, 550 U.S. at __, 82 USPQ2d at 1395-1396). Thus, when considering obviousness of a combination of known elements, the operative question is "whether the improvement is more than the predictable use of prior art elements according to their established functions" ((KSR, 550 U.S. at __, 82 USPQ2d at 1396). "

Applicants allege on p. 15 of the Response of 12/23/08 element (b) of Claim 1 is not taught in the cited art references. Element (b) recites " (b) Modifying the nucleotide sequence to form a modified nucleotide sequence, wherein the modifying is in the region of the nucleotide sequence encoding the C-terminus 18 amino acids of the immunoglobulin heavy chain molecule to remove, or reduce the effectiveness of, one or more vacuolar targeting signal of the encoded immunoglobulin heavy chain;".

Response to Arguments

Frigerio teaches and appreciates that: "...in tobacco the parent IgG tetramers, which do not have free cysteines, are secreted with high efficiency is consistent with the possibility that thiol-mediated retention also occurs in the plant ER. This hypothesis can be tested by mutagenesis or in vivo treatment with reducing agents." (p. 1489, Col. 1, ¶2); and "Vacuolar Delivery Is Caused by Sequences in the IgA/G Tetramer" (p. 1485, Col. 2, ¶2). Frigerio teaches and appreciates that the C-terminal domains in the heavy chain contribute to this localization event because of their own studies where the k light chain is common to both IgG and and IgA?G heavy chain but differ in the heavy chain.

Vitale and Raikhel teach and appreciate "Sequences that are necessary for sorting some vacuolar proteins have been identified (Table 1). If these sequences are deleted by genetic engineering, the vacuolar proteins are secreted. This is in agreement with the hypothesis that no signal is needed for secretion or, alternatively, it indicates that the vacuolar sorting signals are dominant over unidentified secretion sorting signals. Some of these sequences are also sufficient to determine vacuolar sorting once fused to otherwise secreted proteins, and therefore constitute a complete signal (Table 1)" (p. 149, Col. 1, ¶3). The consensus sequences are found in proteins expressed in plants, and "Clearly, there is no easily identifiable general consensus sequence for vacuolar sorting. However, the situation becomes less complicated if we try to assign the proteins to the two types of clearly identified vacuole, the LV and the PSV. The working model shows that signals with an NPIR-like consensus direct proteins to the LV, whereas the less well-defined signals, which are found at the C-terminus, direct proteins to the PSV" (p. 150, Col. 1, ¶2). Vitale and Raikhel teach and appreciate "It is

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now clear that most of the features of sorting to plant vacuoles are novel, and might be unique to plants, for example: • The different mechanisms for the two types of vacuoles. • The signals identified. • The potential receptor for LVs and the process of direct delivery from the ER to PSVs. • The aggregation of storage proteins in early compartments of the secretory pathway." Thus the ordinary artisan would have found that in order to express an antibody in a plant host cell that amino acids found in the C-terminus of recombinant proteins such as an antibody, and overlapping or similar to those amino acids ordinarily found in plant proteins associated with or conferring vacuole signal sorting, would contribute to vacuolization rather than secretion of the recombinant antibody in a plant host cell. Further to have considered modifying the 18 C-terminal amino acids in the constant region of the heavy chain, the ordinary artisan would need only to have considered the residues resembling the vacuole signal sorting residues taught by Vitale and Raikhel, Koide and Matsuoka to modify the amino acid residues in order to eliminate or reduce vacuole targeting and increase secreted antibody production.

Conclusion

17. No claims are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883.

The examiner can normally be reached on 8:00-4:00, Monday through Friday.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/
Examiner, Art Unit 1643
Partial Signatory Authority